

## Supplemental Data

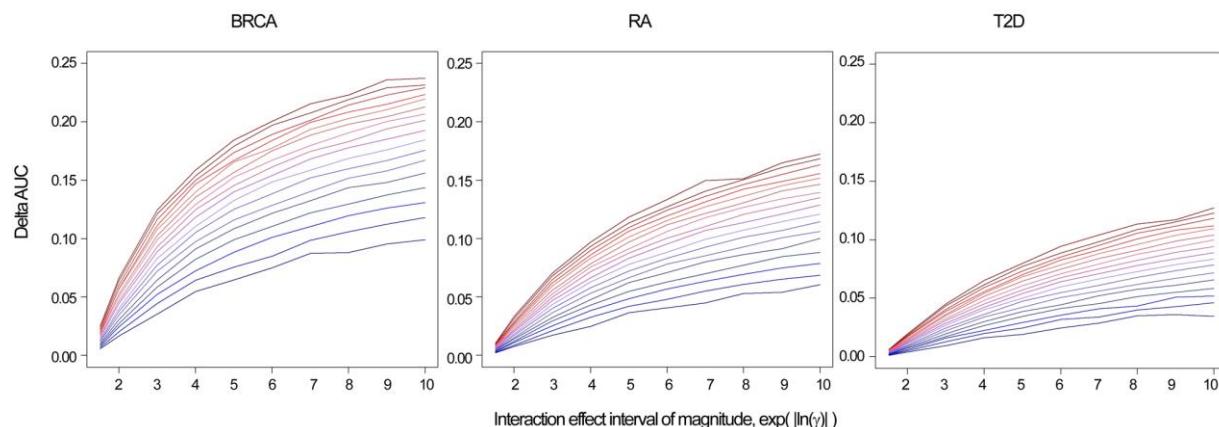
### Inclusion of Gene-Gene and Gene-Environment

### Interactions Unlikely to Dramatically Improve

### Risk Prediction for Complex Diseases

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**Figure S1. Absolute Increase in AUC by the Magnitude of Interaction Effect for Breast Cancer, Rheumatoid Arthritis, and Type 2 Diabetes**



Abbreviations BRCA, RA and T2D indicate respectively breast cancer, rheumatoid arthritis and type 2 diabetes. For each simulation the interaction effects were sampled from a normal distribution such that the effects were in the interval  $[\ln(1/\gamma), \ln(\gamma)]$  with 95% probability. Each model includes 1 to 5 interactions between two known risk alleles, 1 to 5 interactions between a known risk allele and a known environmental exposures, 1 to 5 interactions between a known risk allele and a SNP with no marginal effect and 1 to 5 interactions between a known environmental exposure and a SNP with no marginal effect. Increase in AUC is plotted separately for the total number of interaction (from 4 to 20) and indicated by the color gradient, dark blue representing the presence of 4 interactions and dark red the presence of 20 interactions.

**Table S1. Common Genetic Variants Associated with Invasive Breast Cancer**

SNP	Chromosome	Gene	Risk Allele Frequency in CEU HapMap	Relative Risk per Allele	Discovery Study
rs11249433	1p11.2	<i>EMBP1</i>	0.39	1.16	<i>Thomas et al., 2009</i> <sup>1</sup>
rs13387042	2q35	-	0.50	1.2	<i>Stacey et al., 2007</i> <sup>2</sup>
rs4973768	3p24.1	<i>SLC4A7</i>	0.46	1.11	<i>Ahmed et al., 2009</i> <sup>3</sup>
rs10941679	5p12	-	0.24	1.19	<i>Stacey et al., 2008</i> <sup>4</sup>
rs889312	5q11.2	-	0.28	1.13	<i>Easton et al., 2007</i> <sup>5</sup>
rs13281615	8q24.21	-	0.40	1.08	<i>Easton et al., 2007</i> <sup>5</sup>
rs1011970	9p21.3	<i>CDKN2B-AS1</i>	0.17	1.09	<i>Turnbull et al., 2010</i> <sup>6</sup>
rs865686	9q31.2	-	0.61	1.12	<i>Fletcher et al., 2011</i> <sup>7</sup>
rs10995190	10q21.2	<i>ZNF365</i>	0.85	1.16	<i>Turnbull et al., 2010</i> <sup>6</sup>
rs704010	10q22.3	<i>ZMIZ1</i>	0.39	1.07	<i>Turnbull et al., 2010</i> <sup>6</sup>
rs2981582 <sup>a</sup>	10q26.13	<i>FGFR2</i>	0.40	1.2	<i>Hunter et al., 2007</i> <sup>8</sup>
rs3817198	11p15.5	<i>LSP1</i>	0.30	1.07	<i>Easton et al., 2007</i> <sup>5</sup>
rs614367	11q13.2	-	0.15	1.15	<i>Turnbull et al., 2010</i> <sup>6</sup>
rs3803662	16q12.1	<i>LOC643714</i>	0.27	1.28	<i>Stacey et al., 2007</i> <sup>2</sup>
rs6504950	17q22	<i>STXBP4</i>	0.73	1.05	<i>Ahmed et al., 2009</i> <sup>3</sup>

All SNP selected have been published in the catalog of published genome-wide association studies except the recently discovered SNP rs865686.

<sup>a</sup>For the region 10q26.13, initial discovery identified the SNP rs1219648 with per-allele risk of 1.20, however SNP rs2981579 has been further identified has the most probable risk SNP of this region, we used the per-allele risk from the largest GWAS of Easton et al. that identified this SNP.

**Table S2. Components of the Gail Score**

Gail Components	Relative Risk	Frequencies per Class <sup>a</sup>			
		0	1	2	3
Age at menarche	1.10	0.2072	0.5698	0.2230	-
Number of previous breast biopsies	1.95	0.5563	0.4437	-	-
Age at first child	1.24	0.0082	0.5004	0.3879	0.1036
Number of first degree relatives with breast cancer	1.27	0.8855	0.1092	0.0054	-

<sup>a</sup>Covariates classes are defined as in the Gail score. For age at menarche, classes 0, 1 and 2 correspond to  $\geq 14$ , 12-13 and  $< 12$ . For number of previous breast biopsies, value 0 and 1 correspond to 0 and  $\geq 1$ . For age at first birth, value 0, 1, 2 and 3 correspond to  $< 20$ , 20-24, 25-29 or nulliparous and  $\geq 30$ . For Number of first degree relatives with breast cancer, values 0, 1 and 2 correspond to 0, 1 and  $\geq 2$ .

**Table S3. Common Genetic Variants Associated with Type 2 Diabetes**

SNP	Chromosome	Gene	Risk Allele Frequency in CEU HapMap	Relative Risk per Allele	Discovery Study
rs10923931	1p12	<i>NOTCH2</i>	0.1167	1.14	Zeggini <i>et al.</i> 2008 <sup>9</sup>
rs7578597	2p21	<i>THADA</i>	0.9167	1.15	Zeggini <i>et al.</i> 2008 <sup>9</sup>
rs243021	2p16.1	<i>BCL11A</i>	0.4583	1.09	Voight <i>et al.</i> 2010 <sup>10</sup>
rs2943641	2q36.3	<i>IRS1</i>	0.6083	1.09	Rung <i>et al.</i> 2009 <sup>11</sup>
rs1801282	3p25.2	<i>PPARG</i>	0.9250	1.15	Altshuler <i>et al.</i> 2000 <sup>12</sup>
rs4607103	3p14.1	<i>ADAMTS9</i>	0.8083	1.10	Zeggini <i>et al.</i> 2008 <sup>9</sup>
rs1470579	3q27.2	<i>IGF2BP2</i>	0.2917	1.14	Saxena <i>et al.</i> 2007 <sup>13</sup>
rs10010131	4p16.1	<i>WFS1</i>	0.7333	1.11	Sandhu <i>et al.</i> 2007 <sup>14</sup>
rs4457053	5q14.1	<i>ZBED3</i>	0.2589	1.16	Voight <i>et al.</i> 2010 <sup>10</sup>
rs7754840	6p22.3	<i>CDKAL1</i>	0.3083	1.19	Saxena <i>et al.</i> 2007 <sup>13</sup>
rs864745	7p15.1	<i>JAZF1</i>	0.5175	1.12	Zeggini <i>et al.</i> 2008 <sup>9</sup>
rs972283	7q32.3	<i>KLF14</i>	0.5500	1.10	Voight <i>et al.</i> 2010 <sup>10</sup>
rs896854	8q22.1	<i>TP53INP1</i>	0.4750	1.10	Voight <i>et al.</i> 2010 <sup>10</sup>
rs13266634	8q24.11	<i>SLC30A8</i>	0.7500	1.15	Sladek <i>et al.</i> 2007 <sup>15</sup>
rs10811661	9p21.3	<i>CDKN2A/B</i>	0.7917	1.19	Saxena <i>et al.</i> 2007 <sup>13</sup>
rs13292136	9q21.31	<i>CHCHD9</i>	0.9333	1.20	Voight <i>et al.</i> 2010 <sup>10</sup>
rs12779790	10p13	<i>CDC123/CAMKID</i>	0.2288	1.09	Zeggini <i>et al.</i> 2008 <sup>9</sup>
rs1111875	10q23.33	<i>HHEX/IDE</i>	0.5583	1.17	Saxena <i>et al.</i> 2007 <sup>13</sup>
rs7903146	10q25.2	<i>TCF7L2</i>	0.2500	1.40	Grant <i>et al.</i> 2006 <sup>16</sup>
rs163184	11p15.4	<i>KCNQ1</i>	0.5583	1.09	Yasuda <i>et al.</i> 2008 <sup>17</sup>
rs5215	11p15.1	<i>KCNJ11</i>	0.4083	1.09	Gloyn <i>et al.</i> 2003 <sup>18</sup>
rs1552224	11q13.4	<i>CENTD2</i>	0.8750	1.13	Voight <i>et al.</i> 2010 <sup>10</sup>
rs10830963	11q21	<i>MTNR1B</i>	0.3000	1.13	Prokopenko <i>et al.</i> 2009 <sup>19</sup>
rs1531343	12q14.3	<i>HMGA2</i>	0.1000	1.20	Voight <i>et al.</i> 2010 <sup>10</sup>
rs7961581	12q21.1	<i>TSPAN8/LGR5</i>	0.2333	1.11	Zeggini <i>et al.</i> 2008 <sup>9</sup>
rs7957197	12q24.31	<i>HNF1A</i>	0.8500	1.14	Voight <i>et al.</i> 2010 <sup>10</sup>
rs11634397	15q25.1	<i>ZFAND6</i>	0.5948	1.11	Voight <i>et al.</i> 2010 <sup>10</sup>
rs8042680	15q26.1	<i>PRC1</i>	0.2167	1.10	Voight <i>et al.</i> 2010 <sup>10</sup>
rs9939609	16q12.2	<i>FTO</i>	0.4500	1.12	Frayling <i>et al.</i> 2007 <sup>20</sup>
rs757210	17q12	<i>HNF1B (TCF2)</i>	0.4333	1.12	Gudmundsson <i>et al.</i> 2007 <sup>21</sup>
rs5945326	Xq28	<i>DUSP9</i>	0.7667	1.25	Voight <i>et al.</i> 2010 <sup>10</sup>

**Table S4. Environmental and Clinical Risk Factors of Type 2 Diabetes**

Environmental and Clinical Risk Factors	Relative Risk	Frequencies per Class	
		0	1
BMI ≥ 25	5.10	0.7529	0.2471
Smoking status	1.79	0.7892	0.2108
Physical activity	1.12	0.5626	0.4374
Family history of type 2 diabetes	3.04	0.8398	0.1602

**Table S5. Common Genetic Variants Associated with Rheumatoid Arthritis**

SNP <sup>a</sup>	Chromosome	Gene	Risk Allele Frequency in CEU HapMap <sup>b</sup>	Relative Risk per Allele	Discovery/Replication Study
SE	6p21	<i>DRB1</i> *0401	0.09	3.3	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *0404	0.04	1.85	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *0405	0.00	3.84	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *0408	0.01	1.04	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *0101	0.06	1.6	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *0102	0.01	1.1	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *1001	0.01	2.35	<i>Fernando et al. 2008</i> <sup>22</sup>
SE	6p21	<i>DRB1</i> *09	0.01	1.48	<i>Fernando et al. 2008</i> <sup>22</sup>
rs2476601	1p13.2	<i>PTPN22</i>	0.14	1.75	<i>Begovich et al. 2004</i> <sup>23</sup>
rs3761847	9q33.2	<i>TRAF1-C5</i>	0.48	1.32	<i>Plenge et al. 2007</i> <sup>24</sup>
rs7574865	2q32.3	<i>STAT4</i>	0.21	1.27	<i>Remmers et al. 2007</i> <sup>25</sup>
rs17066662	6q23.3	<i>TNFAIP3</i>	0.83	1.33	<i>Plenge et al. 2007</i> <sup>26</sup>
rs6920220	6q23.3	<i>TNFAIP3</i>	0.18	1.22	<i>Plenge et al. 2007</i> <sup>26</sup>
rs4810485	20q13.12	<i>CD40</i>	0.77	1.15	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs2812378	9p13.3	<i>CCL21</i>	0.35	1.12	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs3087243	2q33.2	<i>CTLA4</i>	0.54	1.11	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs2240340	1p36.13	<i>PADI4</i>	0.43	1.02	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs42041	7q21.2	<i>CDK6</i>	0.29	1.11	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs3890745	1p36.32	<i>TNFRSF14</i>	0.69	1.12	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs4750316	10p15.1	<i>PRKCQ</i>	0.82	1.14	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs1678542	12q13.3	<i>KIF5A</i>	0.63	1.12	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs6822844	4q27	<i>IL2/IL21</i>	0.8	1.09	<i>Raychaudhuri et al. 2008</i> <sup>27</sup>
rs10919563	1q32.1	<i>PTPRC</i>	0.9	1.14	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs11586238	1p13.1	<i>CD2</i>	0.28	1.12	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs1980422	2q33.2	<i>CD28</i>	0.24	1.12	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs394581	6q25.3	<i>TAGAP</i>	0.63	1.1	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs540386	11p12	<i>RAG1</i>	0.87	1.11	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs548234	6q21	<i>PRDM1</i>	0.42	1.1	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs7552317	1q23.3	<i>FCGR2A</i>	0.15	1.12	<i>Raychaudhuri et al. 2009</i> <sup>28</sup>
rs934734	2p14	<i>SPRED2</i>	0.45	1.13	<i>Stahl et al. 2010</i> <sup>29</sup>
rs6859219	5q11.2	<i>ANKRD55, IL6ST</i>	0.78	1.23	<i>Stahl et al. 2010</i> <sup>29</sup>
rs26232	5q21.1	<i>C5orf13, GINI</i>	0.62	1.11	<i>Stahl et al. 2010</i> <sup>29</sup>
rs13315591	3p14.3	<i>PXK</i>	0.08	1.2	<i>Stahl et al. 2010</i> <sup>29</sup>
rs874040	4p15.2	<i>RBPJ</i>	0.37	1.16	<i>Stahl et al. 2010</i> <sup>29</sup>
rs3093023	6q27	<i>CCR6</i>	0.41	1.12	<i>Stahl et al. 2010</i> <sup>29</sup>
rs10488631	7q32.1	<i>IRF5</i>	0.17	1.21	<i>Stahl et al. 2010</i> <sup>29</sup>
rs11676922	2q11.2	<i>AFF3</i>	0.46	1.14	<i>Stahl et al. 2010</i> <sup>29</sup>
rs951005	9p13.3	<i>CCL21</i>	0.86	1.16	<i>Stahl et al. 2010</i> <sup>29</sup>
rs706778	10p15.1	<i>IL2RA</i>	0.45	1.12	<i>Stahl et al. 2010</i> <sup>29</sup>

<sup>a</sup>The SNP list also includes HLA-DRB1 shared epitope (noted SE).<sup>b</sup>Except for the HLA-DRB1 alleles, for which frequencies have been derived from the Nurse's Health Study.<sup>30</sup>

**Table S6. Clinical and Environmental Risk Factors of Rheumatoid Arthritis**

Environmental Factors	Relative Risk	Frequencies per Class	
		0	1
Ever smoker (current or past)	1.59	0.44	0.56
Breast feeding	0.79	0.63	0.37

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